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ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Application No.	Applicant(s)
10/507,923	SZPIRER ET AL.
Examiner	**Art Unit**
Kevin K. Hill, Ph.D.	1633

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 18-40* is/are pending in the application.

4a) Of the above claim(s) *19-21,25,28-34 and 36-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,18,22-24,26,27 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant's response to the Requirement for Restriction, filed on September 24, 2007 is acknowledged.

Applicant has elected without traverse the invention of Group I, Claims 15-24 and 26-28, drawn to a recombinant cell or organism having incorporated into genome i) a genetic construct a nucleotide sequence encoding a toxic molecule, and ii) a genetic sequence encoding an antidote molecule to said toxic molecule.

Within Group I, Applicant has elected with traverse the following restricted embodiments:

a), wherein the genetic construct does not comprise a selectable marker, as recited in claim 15(i),

b) wherein the genetic sequence encoding the antidote is not added to the construct, as recited in claim 15(ii),

c) wherein the toxic molecule is ccdB, as recited in claim 18,

d) wherein the biological organism is a yeast, as recited in claim 22,

e) wherein the non-toxic compound is an exogenous compound, as recited in claim 24,

f) wherein the cell compartment comprising a genome within which the genetic construct is integrated is a chloroplast, as recited in claim 27, and

g) wherein the selectable marker is bordered by two different toxic genes, as recited in claim 28.

Applicant argues that the special technical feature is a eucaryotic cell that includes a genetic sequence encoding a non-native antidote molecule to a poison protein from a poison antidote group, the poison protein being encoded by nucleotide sequence under control of an inducible operator/promoter that is incorporated into the genome of the cell. Applicants would like to point out that the poison proteins recited in claim 18, while not being obvious variants of each other, are related by both phylogenetically and by their mode of action. In particular, these

proteins and their corresponding antidotes all form a group of procaryotic proteins referred to a plasmid addiction systems.

Applicants' arguments have been fully considered but are not found persuasive.

As a first matter, Norris et al (U.S. Patent No. 6,271,359) discloses (see below) the use of poison/antidote genetic systems in eukaryotic cells, and thus the claimed special technical feature does not contribute over the prior art.

As a second matter, MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the Examiner must examine them on the merits, even though they include claims to independent or distinct inventions." In the instant case a serious burden exists since each limitation, directed to a taxonomically distinct biological cell/organism, e.g. plant, yeast, insect, mammal, etc... , directed to a non-obvious toxic/antidote genetic system, and a plurality of transformation vectors comprising distinctly different functional components, e.g. selectable marker, requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. Furthermore, a search and examination of all the claims directed to all claimed embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claimed limitations in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

Amendments

In the reply filed September 24, 2007, Applicant has cancelled Claims 1-14 and 17, withdrawn Claims 25 and 29-33, amended Claims 15, 18, 24 and 27-28, and added new claims, Claims 34-40.

Claims 19-21, 25, 28-34 and 36-40 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 15-16, 18, 22-24, 26-27 and 35 are under consideration.

Priority

This application is a 371 of PCT/BE03/00045, filed March 19, 2003. Applicant's claim for the benefit of a prior-filed parent provisional application 60/365,938, filed on March 19, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

The disclosure of the prior-filed application, 60/365,938, filed on March 19, 2002, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, 60/365,938 does not support claim 27, wherein the genetic construct is integrated into the genome of a specific cell compartment, specifically a chloroplast. Rather, the provisional application discloses integration into the nuclear genome. A certified copy of PCT/BE03/00045 has not been filed with the instant application so as to allow the Examiner to ascertain whether claim 27 is supported as of March 19, 2003. Accordingly, the effective priority date of claim 27 is granted as the filing date of the instant application, July 19, 2005. If Applicant believes the earlier applications provide support for this disclosure, Applicant should point out such support by page and line number in the reply to this Action.

Claims 15-18, 22-24, 26, 28 and 35 are supported by the disclosure of 60/365,938, filed on March 19, 2002. Accordingly, the effective priority date of claims 15-18, 22-24, 26, 28 and 35 is granted as March 19, 2002.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on September 16, 2004, June 29, 2006, and September 24, 2007, providing more than 140 references. The Examiner was able to consider these to the extent of time allowable. The citations #21 and #112 have been lined through because the citations are incomplete. The signed and initialed PTO Forms 1449 are mailed with this action.

Claim Objections

1. **Claim 18 is objected to because of the following informalities:** The claim identifies *ccdB* as a toxic gene that may be used in the claimed invention. However, the claims do not first identify the toxic gene by its complete name prior to using its acronym. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses, e.g. Epidermal Growth Factor (EGF). Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. **Claims 15-16, 18, 22-24, 26-27 and 35 are rejected under 35 U.S.C. 101** because the claimed invention is not supported by either a specific or substantial utility.

According to the Revised Utility Examination Guidelines (see the Federal Register, Vol. 66, No. 4, pp. 19092-1099; January 5, 2001; also available at http://uspto.nov/web.menu.utility.pdf) the following definitions of specific, and substantial apply.

Specific Utility

A "specific utility" is specific to the subject matter claimed and can "provide a well-defined and particular benefit to the public." *In re Fisher*, 421 F.3d 1365, 1371, 76 USPQ2d 1225, 1230 (Fed. Cir. 2005). This contrasts with a *general* [emphasis added] utility that would be applicable to the broad class of the invention.

Substantial Utility

"[A]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the substantial utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Fisher*, 421 F.3d at

1371, 76 USPQ2d at 1230. A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility. See also MPEP 2107-2107.02, and *Brenner Comr. Pats. v. Manson,* 148 USPQ 689 (US SupCt 1966).

The specification does not support a credible, specific and substantial utility because the specification does not teach a transgenic eukaryotic cell or organism genetically modified by the inventive poison/antidote genetic system that is useful to the public in its current form. In the instant case, the specification discloses that the present invention is related to poison/antidote genetic systems for the selection of genetically modified eukaryotic cells. The present invention aims to provide method and means for the characterization and the selection of genetically modified cells and pluricellular organisms that have correctly integrated foreign, exogenous DNA fragment(s) into their genome, and allow the selection of said cells and organisms obtained by rare homologous recombination events (pg 2, [0008-0009]). The combination of a toxic gene with an inducible promoter in a plant cell opens the possibility to use the toxic gene as an efficient and entirely transgenic-line specific herbicide (pg 7, [0030]). The present invention could be improved by the introduction (within or separately from the exogenous above-mentioned genetic construct) of a sequence encoding the poison target (pg 9, [0042]).

The disclosed utilities are not considered credible, specific and substantial because the claims encompass about 250,000 species of eukaryotic protists, about 100,000 species of fungi, about 250,000 species of plants and about 1,000,000 species of animals (waynesword.palomar.edu/trfeb98.htm, last visited November 26, 2007). Thus, no specific utility has been established for the about 1,600,000 eukaryotic species. Furthermore, the claimed genetically modified eukaryotes are just invitations for one skilled in the art to figure out how a gene of interest functions or what the biological activities are for the claimed invention, clearly indicated by the phrases "opens the possibility" (pg 7, lines 4-5) and "could be improved" (pg 8, lines 20-21). While methods of researching a gene of interest in a transgenic cell or organism may ultimately be of value to the scientific and medical arts, this use is not considered a specific,

substantial or practical utility because it does not provide some "real-world" value or immediate benefit to the public. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Labels such as "for research purposes" are not helpful in determining if an Applicant has identified a specific and substantial utility for the invention.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use Applicants' alleged discovery, not how to find out how to use it for themselves. The instant application has failed to provide guidance as to the identity of all of the toxic genes and their corresponding antidote genes embraced by the generic claim, and how one of skill in the art could use the claimed invention of nucleic acids in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points to create an enormous plurality of distinctly different genetically modified eukaryotic organisms for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson,* 148 USPQ at 696.

3. **Claims 15-16, 18, 22-24, 26-27 and 35 are also rejected under 35 U.S.C. 112, first paragraph**. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility for the reasons set forth above, one skilled in the art clearly would not know **how to use** the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 15-16, 18, 22-24, 26-27 and 35 are rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a genetically modified cell or organism comprising a genetic construct comprising a nucleotide sequence encoding a toxic gene and a genetic sequence encoding an antidote (or anti-toxic) molecule. At issue for the purpose of written description requirements is the lack of adequate written description for the claimed genus of "toxic genes/poison proteins", the claimed genus of "antidote or anti-toxic genes", and the claimed genus of recombinant eukaryotic cells capable of generating transgenic multicellular organisms.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure.

With respect to the toxic genes and anti-toxic genes, the specification does not define the term "toxic gene", and thus the claimed genetic construct encoding toxic genes reasonably embraces an enormous genus of structurally distinct and undisclosed molecules. Furthermore, the claimed invention requires a nucleic acid encoding an "antidote gene" so as to suppress the enormous genus of structurally distinct and undisclosed toxic molecules. Rather, the specification discloses that the toxic genes/anti-toxic genes are, respectively: CcdB/CcdA, Kid/Kis, Doc/Phd, PemK/PemI and Hok/SoK (pg 5, [0023-0024]). However, the specification does not disclose the antidote/anti-toxic genes for the toxic genes ParE, RelE, or MazE. Rather, the bacterial targets for the toxic molecules such as MazE, ParE, ChpAK/MazF and ChpBK have not even been identified (Couturier et al., Trends in Microbiology 6:269-275, 1998; *of record in IDS, #42). Without a correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

With respect to the genus of genetically modified eukaryotic cells and organisms, Applicant contemplates the present invention to be suitable for yeast, animal cells, e.g. mammalian and insect (pg 6, [0029]), and plant cells. The specification discloses transgenic plants. However, the specification fails to teach or describe non-human "totipotent" cells to be utilized in methods for obtaining genetically modified non-human pluricellular organisms. The ES cell technology is generally limited to the mouse system, and that only "putative" ES cells exist for other species (Moreadith et al., J. Mol. Med. 75:208-216, 1997; Summary on page 214; *of record in IDS, #79). Likewise, Mullins et al. (J. Clin. Invest. 98:S37-S40, 1996; *of record in IDS, #80) stated that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell has been successfully demonstrated" (pg S38, col. 1, ¶1). The instant specification also fails to provide a representative number of species for a broad genus of a eukaryotic host cells as claimed as well as a representative number of species for a broad genus of a non-human totipotent cell capable of generating a genus of transgenic non-human eukaryotic organisms. The

instant specification fails to provide and describe the essential characteristics for a representative number of species for a broad genus of a non-human totipotent cells. What are the essential characteristics of other non-human cell lines that had not yet been shown capable of regenerating an entire pluricellular organism from a single totipotent cell at the filing date of the present application?

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200,

1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the nucleotide sequences which encode toxic and antidote genes as contemplated in the specification, nor the identity of non-human totipotent cells capable of giving rise to pluricellular non-human organisms encompassed by the claims. Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the broad genus of "toxic genes/poison proteins", "antidote or anti-toxic genes", and recombinant eukaryotic cells capable of generating transgenic multicellular organisms at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

5. **Claims 15-16, 18, 22-24, 26-27 and 35 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing about 250,000 species of eukaryotic protists, about 100,000 species of fungi, about 250,000 species of plants and about 1,000,000 species of animals (waynesword.palomar.edu/trfeb98.htm, last visited November 26, 2007).

The claims are also broad for encompassing an enormous genus of structurally distinct and undisclosed molecules toxic to a given cell type, and an at least equally enormous genus of structurally distinct and undisclosed anti-toxin genes not known in the art at the time of filing, wherein the genetic sequence encoding the toxin and anti-toxin genes are described only by the function of the respective gene products.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells, plant cells, mammalian cell lines and insect cells.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

With respect to the toxic genes and anti-toxic genes, the specification discloses that the toxic genes/anti-toxic genes are, respectively: CcdB/CcdA, Kid/Kis, Doc/Phd, PemK/PemI and Hok/SoK (pg 5, [0023-0024]). Apart from the disclosure of a prokaryote host cell possessing a mutation in which arginine 462 is replaced by a cysteine in the amino acid sequence of the GyrA polypeptide of the gyrase that renders the host cell resistant to the toxic activity of the bacterial poison CcdB molecule (pg 6, [0027]; pg 8, [0043-44]), the instant specification fails to teach any other mutation or a combination of mutations that confer resistance to the toxic activity of any two different bacterial toxic molecules. The specification does not disclose the antidote/anti-toxic genes for the toxic genes ParE, RelE, or MazE.

With respect to the genus of genetically modified eukaryotic cells and organisms, Applicant contemplates the present invention to be suitable for yeast, animal cells, e.g. mammalian and insect (pg 6, [0029]) and plant cells. Apart from the mouse embryonic stem cell known in the prior art, the specification fails to teach any other non-human totipotent cells may be used so that non-human pluricellular organisms derived from such genetically modified totipotent cells could be obtained.

The present invention is based upon a genetic construct which comprises a toxic gene, preferably a poison, under the control of an inducible promoter/operator genetic sequence and a genetic sequence encoding an antidote molecule, said genetic construct being introduced into a eucaryote cell or eucaryote organism. What is the purpose(s) of the genetically modified cell/organism? It is also apparent from the present disclosure that, at the effective filing date of the present application, no genetically modified pluricellular organism has been generated using the claimed toxin/antidote genetic system. Enablement requires the specification to teach how to make and use the claimed invention, the instant specification fails to teach a skilled artisan on how to use such a transgenic eukaryotic cell or organism.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The specification does not disclose the antidote/anti-toxic genes for the toxic genes ParE, RelE, or Doc. At about the effective filing date of the present application (March 19, 2002), apart from the known CcdB resistant prokaryote host cell which possesses a mutation in which arginine 462 is replaced by a cysteine in the amino acid sequence of the GyrA polypeptide of the gyrase, nothing was known in the prior art on other prokaryotic host cells possessing another mutation, let alone for mutations which confer resistance to the toxic activity of two different toxic molecules to a prokaryote cell as evidenced by the teachings of Jensen et al. (Molecular Microbiology 17:205-210, 1995; *of record in IDS #65) and Couturier et al. (Trends in Microbiology 6:269-275, 1998; *of record in IDS, #42). Rather, the bacterial targets for the toxic molecules such as MazE, ParE, ChpAK/MazF and ChpBK have not even been identified. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present specification to do so. Otherwise, it would have required a large quantity of trial and error experimentation by a skilled artisan to obtain a prokaryote host cell as broadly claimed. Moreover, the physiological art is recognized as unpredictable (MPEP §2164.03).

Additionally, at about the effective filing date of the present application the ES cell (a totipotent cell) technology was generally limited to the mouse system, and that only "putative" ES cells exist for other species (Moreadith et al., 1997; pg 214, Summary, IDS #79). Seamark (Reprod. Fertil. Dev. 6:653-657, 1994; *of record in IDS #103) also reported that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract). Likewise, Mullins et al. (1996, IDS #80) stated that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell has been successfully demonstrated" (pg S38, col. 1, ¶1). Furthermore, the transgenic art is highly unpredictable with respect to the attainment of a desired phenotype as evidenced by the teachings of Hammer et al. (J. Anim. Sci. 63:269-278, 1986; *of record in IDS #57), Ebert et al. (Molecular Endocrinology 2:277-283, 1988; *of record in IDS #44). Particularly, the attainment of a desired phenotype arising from the disruption of a particular

gene through homologous recombination is unpredictable. Moreadith et al. (1997; IDS #79) supported phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discussed that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. reported that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (pg 208, col. 2, ¶2).

Concerns regarding the position of genome insertion of a polynucleotide encoding a genetic construct comprising the poison/antidote genetic system as well as a desired gene of interest are important because the position may influence the phenotype of the transgenic cell/organism. The phenotype of the transgenic cell/organism is a necessary element that the specification must teach to enable one skilled in the art concerning how to use the transgenic cell/organism for its disclosed utility when considering the enablement of the invention. Without any phenotype, one skilled in the art would not know how to use the claimed transgenic cell/organism even though its genome comprises a transgene embraced by the claims.

One of skill would not be able to rely on the state of the transgenic art or the teaching of the specification to predictably produce transgenic cells/organisms for the breadth claimed. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome, which would vary among different species of animals. The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, J. Biotech. 34: 269-287, 1994; pg 281).

The mere capability to perform gene transfer in a given species is not enabling for the claimed genus of transgenic animals because the desired phenotypes cannot be predictably achieved simply because the animal has the desired genotype. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA

methylation or deletion from the genome (Kappel et al, Current Opinion in Biotechnology 3: 548-553, 1992; pg 549, col. 2, ¶ 2). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall, Theriogenology 45: 57-68, 1996; pg 61, ¶2, line 9 to pg 62, line 3). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues. Additional factors influencing low expression, or the lack there of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct. These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron, Molec. Biotech. 7: 253-265, 1997; pg 256, lines 3-13, col. 1-2, joining ¶).

Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund, Arteroscler. Throm. Vasc. Biol. 20: 1425-1429, 2000; pg 1426, col. 1, ¶ 1, lines 1-7). Similarly, Anders and Schlondorff (Exp. Nephrol. 8: 181-193, 2000) teach that:

> "[A]nimal models of human renal disease depend heavily of the [mouse] genetic background. Attention to the genetic background and appropriate back-crossing are, therefore, of great importance in the design and interpretation of experimental studies, especially in transgenic mice." (pg 181, Abstract).

> "The problem of an undefined genetic background in transgenes also includes the lack of adequate controls. Because of marked polymorphism in the genetic background of many laboratory mouse strains, it cannot be concluded that the null mutation is the only cause for a phentoypical change. This problem is widely underappreciated, since in early backcross generations, even hybrid littermate controls are genetically different at the targeted gene locus and other gene loci. (pg 182, col.s 1-2, joining ¶).

The level of one of ordinary skill in the transgenic art is considered to be high. It is not apparent as to how one skilled in the art reasonably correlates, without undue experimentation, between a transgenic yeast or mouse and an enormous genus of transgenic non-human animals, e.g., elephants, monkeys, dogs, cats, cows, chimpanzees, insects, lizards, frogs, birds, capybaras, etc, particularly in view of the foregoing reasons.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

The instant specification fails to disclose genetically modified eukaryotic host cells possessing mutations or genes which confer resistance to the toxic activity of two different bacterial toxic molecules. Nor does the *present* disclosure provide for an enormous genus of non-human totipotent cells to derive genetically modified non-human organisms that have a desired or useful *phenotype*. Thus, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the transgenic art and physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

6. **Claims 15-16, 18, 22-24, 26-27 and 35 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to claim 15(i), the claim recites the phrase "its genome" in 15(i). Given the grammatical structure of the claim, the genetic construct of 15(i) is the subject to which the

pronoun "it" refers, and thus it is unclear how a genetic construct incorporates itself into its own genome.

With respect to claim 15(i), the claim requires the poison protein to be selected from a poison/antidote group. However, if the protein is an antidote protein, then by definition, the protein is not a poison. Furthermore, the claim does not set forth the species of poison and antidote proteins within the claimed group.

With respect to claim 15(ii), the phrase "not natively present" is not defined. Furthermore, how can a recombinant cell/organism express a nucleic acid sequence encoding a gene product if said nucleic acid sequence is "not natively present" in the cell? The processes of transcription and translation are inherently and natively present within a cell.

Dependent claims are included in the basis of the rejection because although they recite and encompass the genetic construct, the poison proteins and the antidote proteins, they do not clarify the nature of the structural limitations of the genetic construct, how an antidote protein is to become a poison protein, nor what is or is not native.

Examiner's Note

The Examiner is aware of the apparent contradiction between applying the 35 U.S.C. 112, first paragraph, lack of enablement rejection presented above and the following 35 U.S.C. 102 and 103 art rejections. For the sake of compact prosecution, all issues relating to the instant application will be set forth in the First Action on the Merits. The art rejections are applied for disclosing knowledge in the art prior to the filing of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. **Claims 15-16, 18, 22-24, 26 and 35 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e)** as being anticipated by Norris et al (U.S. Patent No. 6,271,359).

With respect to claim 15, Norris et al disclose eukaryotic cells comprising a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, wherein said toxic gene is under the control of an inducible promoter, the eukaryotic cell further comprising an anti-toxic genetic sequence encoding an antidote molecule to the poison protein, wherein said antidote molecule is a heterologous ("not natively present") in said eukaryotic cell (col. 8, lines 35-39; col. 30, lines 46-50).

With respect to claim 16, the genetic sequence encoding the antidote molecule is under the control of an inducible promoter/operator genetic sequence (col. 6, lines 15-24; col. 8, lines 35-37; col. 29, lines 45-53).

With respect to claim 18, the toxic gene is CcdB (col. 13, line 34).

With respect to claim 22, the eukaryotic cell may be a yeast cell (col. 5, lines 9-12), the instantly elected transgenic cell/organism.

With respect to claims 23-24, Norris et al disclose the inducible promoter/operator genetic sequence is induced by an exogenous, non-toxic compound, e.g. isopropyl β-D-thiogalactopyranoside (IPTG) (col. 39, Example 6, lines 50-52).

With respect to claim 26, Norris et al contemplate a genus of eukaryotic expression vectors (col. 19, lines 1-57), including such genome integrative vectors as baculoviral vectors, tobacco mosaic viral vectors, Ti plasmids, and retroviral vectors (col. 25, lines 21-30), as well as non-integrating vectors (col. 25, lines 43-46).

With respect to claim 35, the genetic sequence encoding the antidote is an episomal DNA, Norris et al contemplate a genus of eukaryotic expression vectors (col. 19, lines 1-57), including non-integrating vectors (col. 25, lines 43-46).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. **Claims 15-16, 22-24, 26 and 35 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) in view of Parekh et al (Biotechnol. Prog. 12:16-21, 1996).

Determining the scope and contents of the prior art.

Kristoffersen et al teach a genetically modified yeast having a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, specifically *relE*, under the control of an inducible promoter, specifically GAL1, whereupon expression of *relE* is induced by exogenous, non-toxic compound, galactose, said yeast further comprising a genetic sequence encoding an antidote molecule, specifically *relB*, wherein the art recognizes the prokaryotic *relB* as "not present natively" in yeast, and wherein the genetic sequence encoding the antidote molecule is under the control of an inducible promoter, specifically MET25, whereupon the expression of *relB* is induced by the absence of methionine (pg 5525, col. 1, last ¶), wherein the art recognizes the pYES2 expression vector to be an episomal DNA.

Kristoffersen et al do not teach the genetic construct to be integrated into the genome of the host cell. However, at the time of the invention, Parekh et al taught the use of yeast transformation vectors that integrate into the yeast genome for stable transformation.

Ascertaining the differences between the prior art and the claims at issue.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of integrating and non-integrating yeast transformation vectors. Furthermore, the use of a poison/antidote genetic system had been practiced in yeast cells.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have both the practical experience in molecular biology and the creation of transgenic cells and organism. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a non-integrating yeast transformation vector as taught by Kristoffersen et al with an integrating yeast transformation vector as taught by Parekh et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute an episomal transformation vector with an integrating transformation vector because the integrating vector would be stably and predictably propagated into each daughter cell.

Thus, the invention as a whole is *prima facie* obvious.

9. **Claims 15 and 18 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) and Parekh et al (Biotechnol. Prog. 12:16-21, 1996), as applied to claims 15-16, 22-24, 26 and 35, and in further view of Norris et al (U.S. Patent No. 6,271,359).

Determining the scope and contents of the prior art.

Neither Kristoffersen et al nor Parekh et al teach the toxic gene to be CcdB. However, at the time of the invention, Norris et al disclosed eukaryotic cells, e.g. yeast cells (col. 5, lines 9-12), the instantly elected transgenic cell/organism, comprising a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, wherein said toxic gene is under the control of an inducible promoter, the eukaryotic cell further comprising an anti-toxic genetic sequence encoding an antidote molecule to the poison protein, wherein said antidote molecule is a heterologous ("not natively present") in said eukaryotic cell (col. 8, lines 35-39; col. 30, lines 46-50). The genetic sequence encoding the antidote molecule is under the control of an inducible promoter/operator genetic sequence (col. 6, lines 15-24; col. 8, lines 35-37; col. 29, lines 45-53) that is induced by an exogenous, non-toxic compound, e.g. isopropyl β-D-thiogalactopyranoside (IPTG) (col. 39, Example 6, lines 50-52). Norris et al contemplated a genus of eukaryotic expression vectors (col. 19, lines 1-57), including such genome integrative vectors as baculoviral

vectors, tobacco mosaic viral vectors, Ti plasmids, and retroviral vectors (col. 25, lines 21-30), as well as non-integrating vectors (col. 25, lines 43-46). Furthermore, the genetic sequence encoding the antidote is an episomal DNA or non-integrating vectors (col. 25, lines 43-46). Norris et al disclosed the toxic gene CcdB (col. 13, line 34).

Ascertaining the differences between the prior art and the claims at issue.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as their use in eukaryotic yeast cells.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a relE/relB poison/antidote genetic system as taught by Kristoffersen et al with a CcdB/CcdA poison/antidote genetic system as taught by Norris et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute one poison/antidote genetic system for another as a matter of optimizing the transformation and stable propagation of a transformation vector in a desired eukaryotic cell type.

Thus, the invention as a whole is *prima facie* obvious.

10. **Claims 15 and 27 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000), Parekh et al (Biotechnol. Prog. 12:16-21, 1996) and Norris et al (U.S. Patent No. 6,271,359), as applied to claims 15-16, 18, 22-24, 26 and 35, and in further view of Newman et al (Mol. Gen. Genet. 230(1-2):65-74, 1991; Abstract only) and Rochaix (Ann. Rev. Genet. 29: 209-230, 1995).

Determining the scope and contents of the prior art.

Neither Kristoffersen et al, Parekh et al, nor Norris et al teach the genetic construct to be integrated into the chloroplast genome of the host cell. However, at the time of the invention, Newman et al taught the ability to genetically transform the chloroplast genome of the *Chlamydomonas reinhardtii* with an integrating transformation vector, wherein the art recognizes *C. reinhardtii* to be a photosynthetic yeast (Rochaix).

Ascertaining the differences between the prior art and the claims at issue.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as chloroplast transformation vectors and protocols in photosynthetic yeasts.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a nuclear integrating transformation vector as taught by Norris et al with a chloroplast integrating transformation vector as taught by Newman et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute one integrating transformation vector for another as a matter of optimizing the transformation and stable propagation of a transformation vector in a desired eukaryotic cell type.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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